Introduction to TMS
TMS Basics

Alvaro Pascual-Leone, MD, PhD

Senior Scientist, Hinda and Arthur Marcus Institute for Aging Research
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Harvard Medical School

Marcus Institute for Aging Research
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HARVARD MEDICAL SCHOOL AFFILIATE

TMS Basics

- Misnomer

- Stimulation to brain interaction
  - Brain structure
  - Brain state

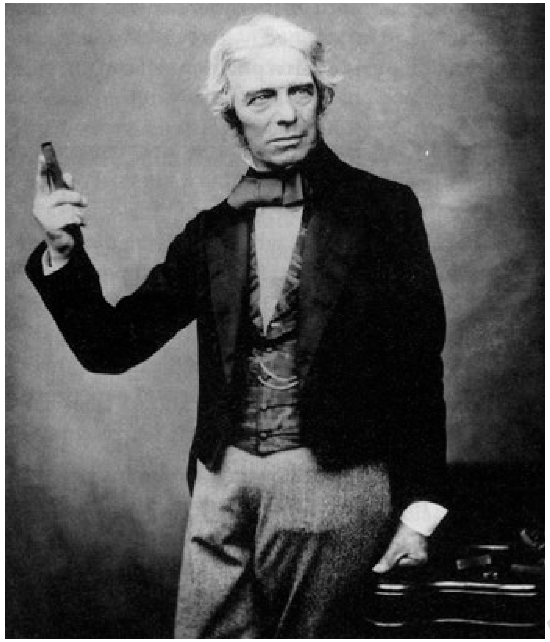
- Pulse shape

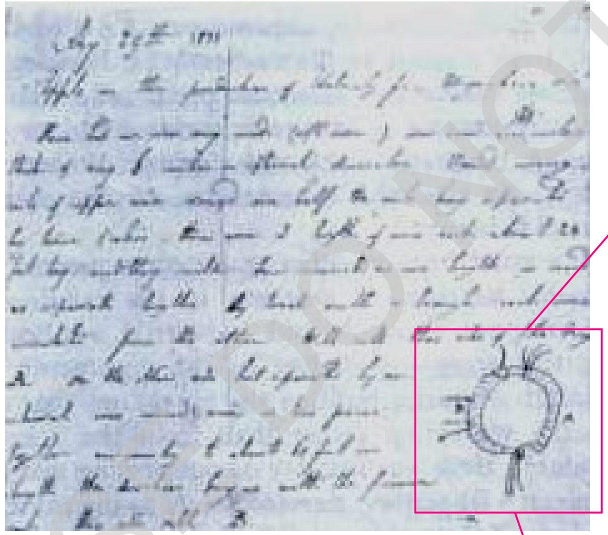
- Single pulse
- Pairs of pulses
- Trains of repetitive pulses

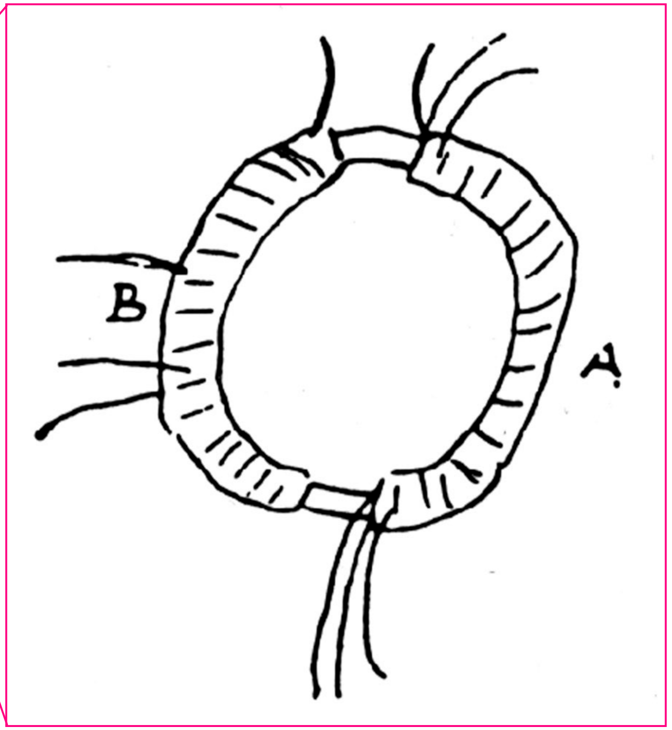
- Variability

Electro-Magnetic Induction

"I think I got hold of a good thing"

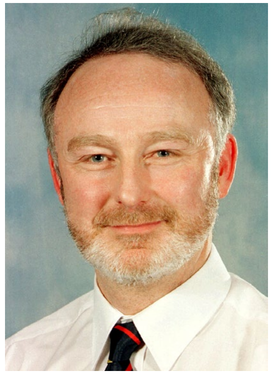






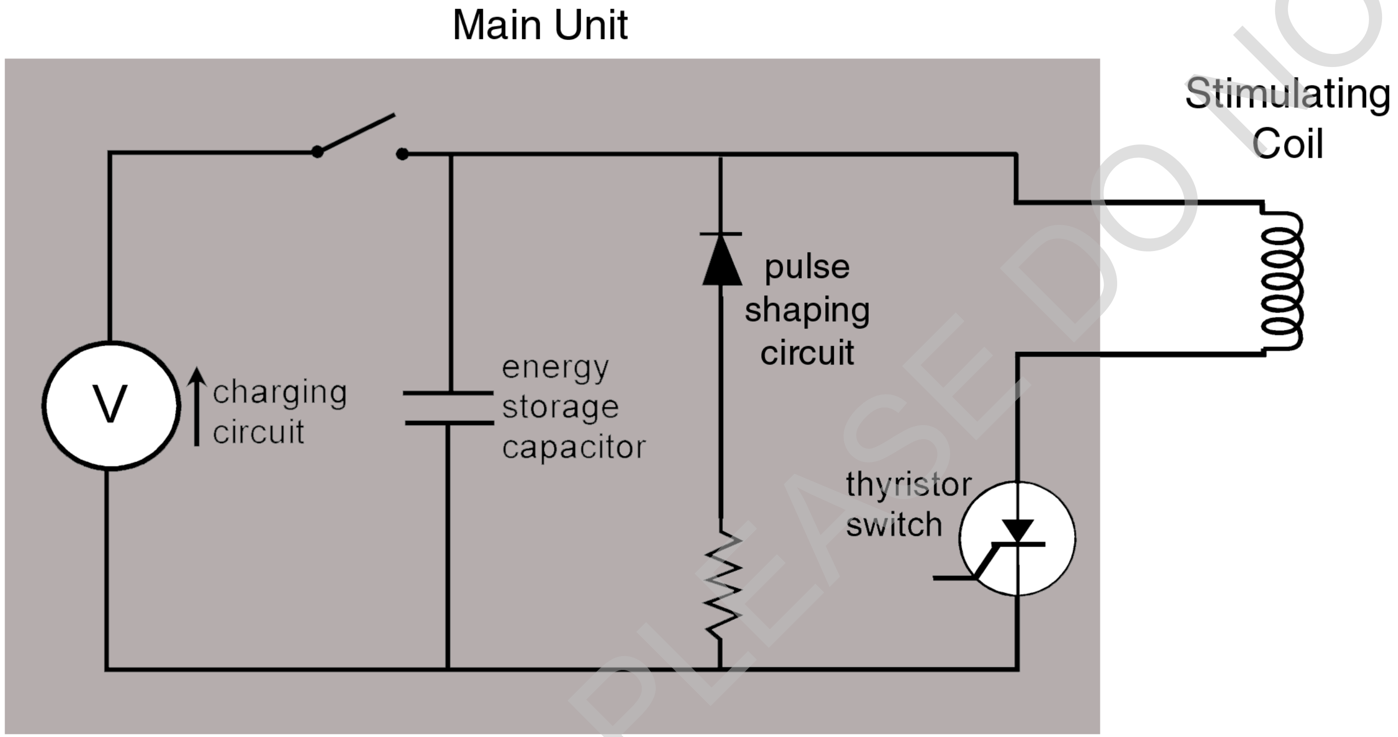
M. Faraday

29 August 1831



Anthony Barker

1984

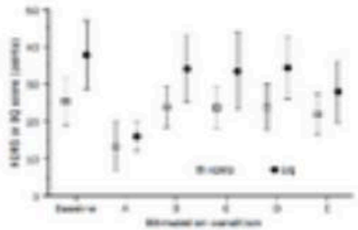


Origin of Therapeutic TMS – Repetitive TMS

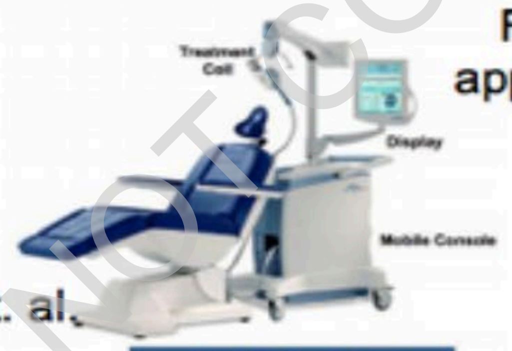
1984 | 1987 | 1996 | 2007 | 2008 | 2012

Anthony Barker
Single Pulse TMS

Cadwell
Repetitive TMS
(rTMS)

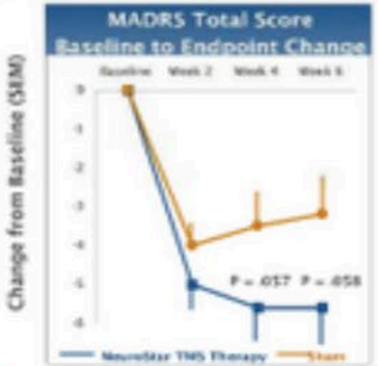


Pascual-Leone, et. al,
George, et. al.
rTMS for depression

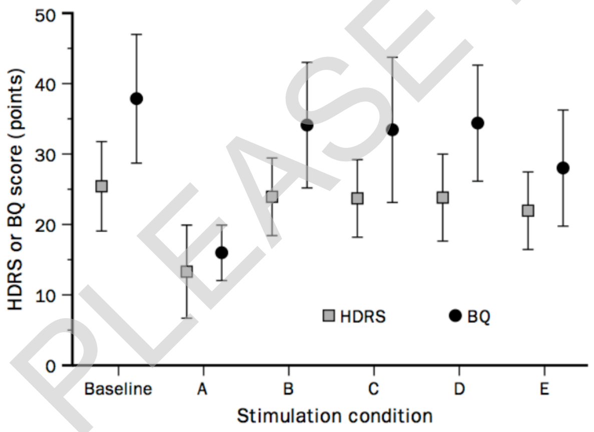


FDA
approval

NHIC
Medicare
Approval
(MA,NH,VT and
RI)



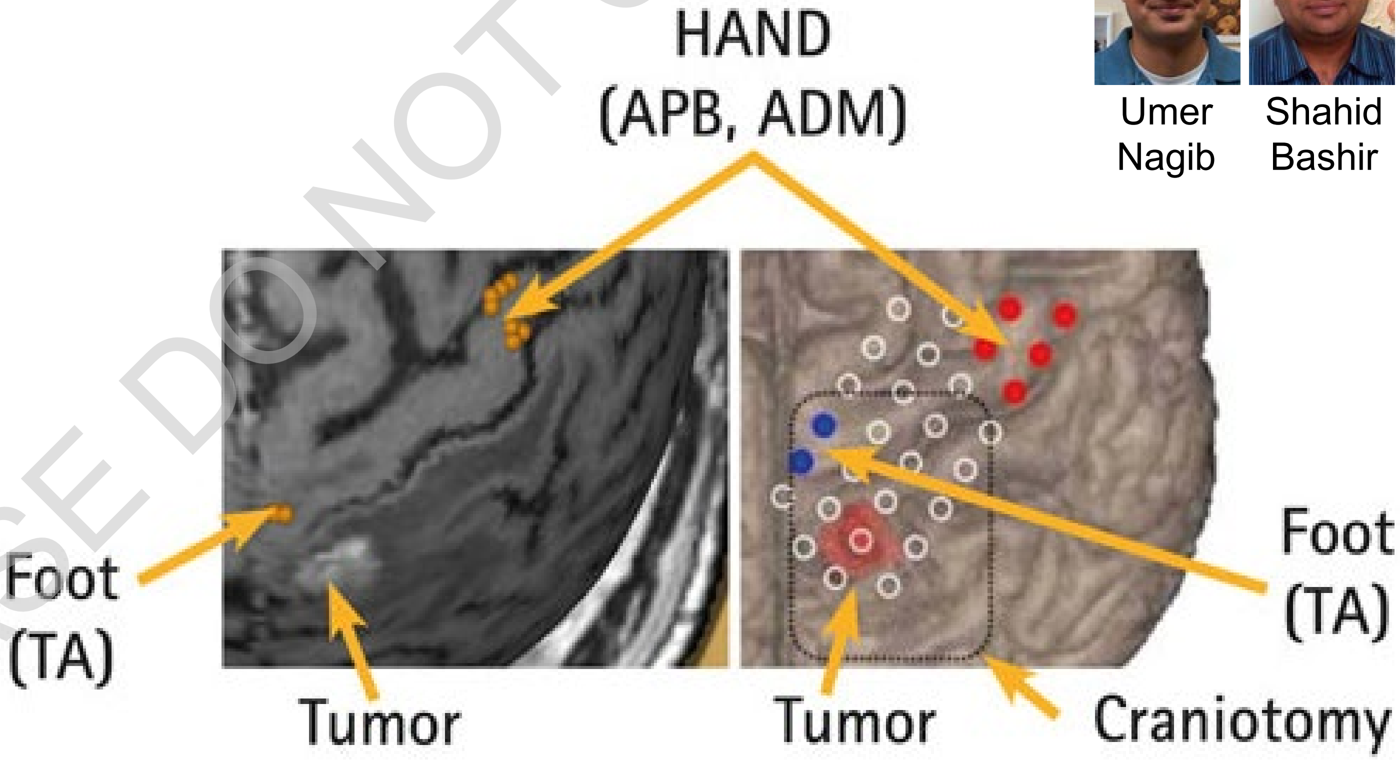
Neuronetics Phase III
trial of rTMS for
Medication-resistant
depression



Pascual-Leone et al. The Lancet 1996

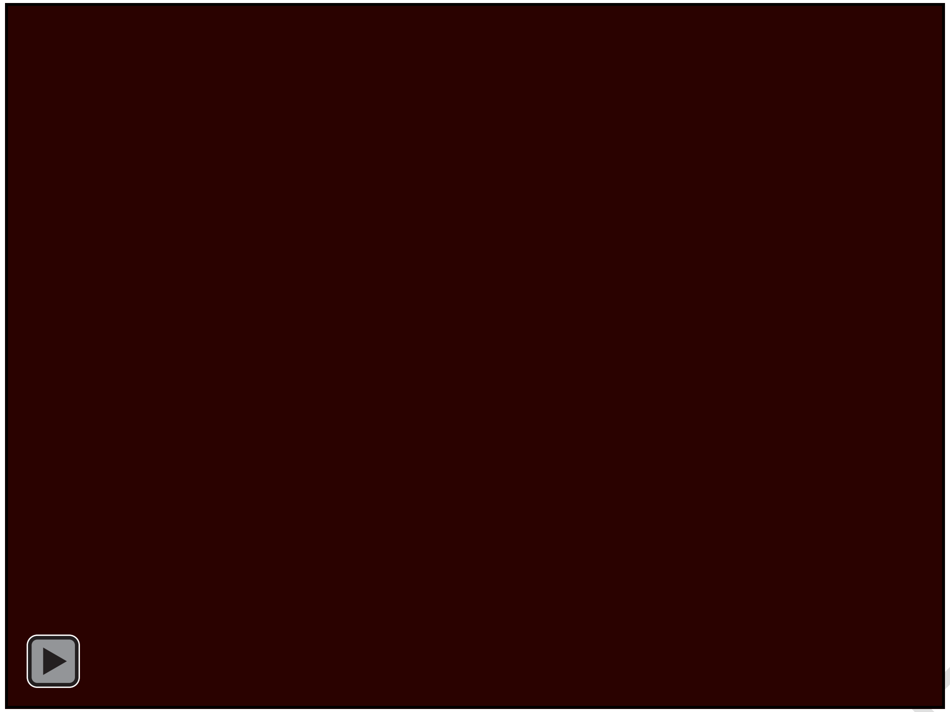
Nexstim

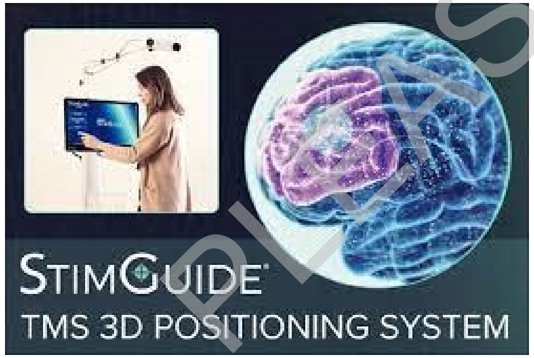
FDA approved for cortical mapping (motor & speech)



Umer Nagib | Shahid Bashir | Alex Golby

FDA Cleared Neuronavigation

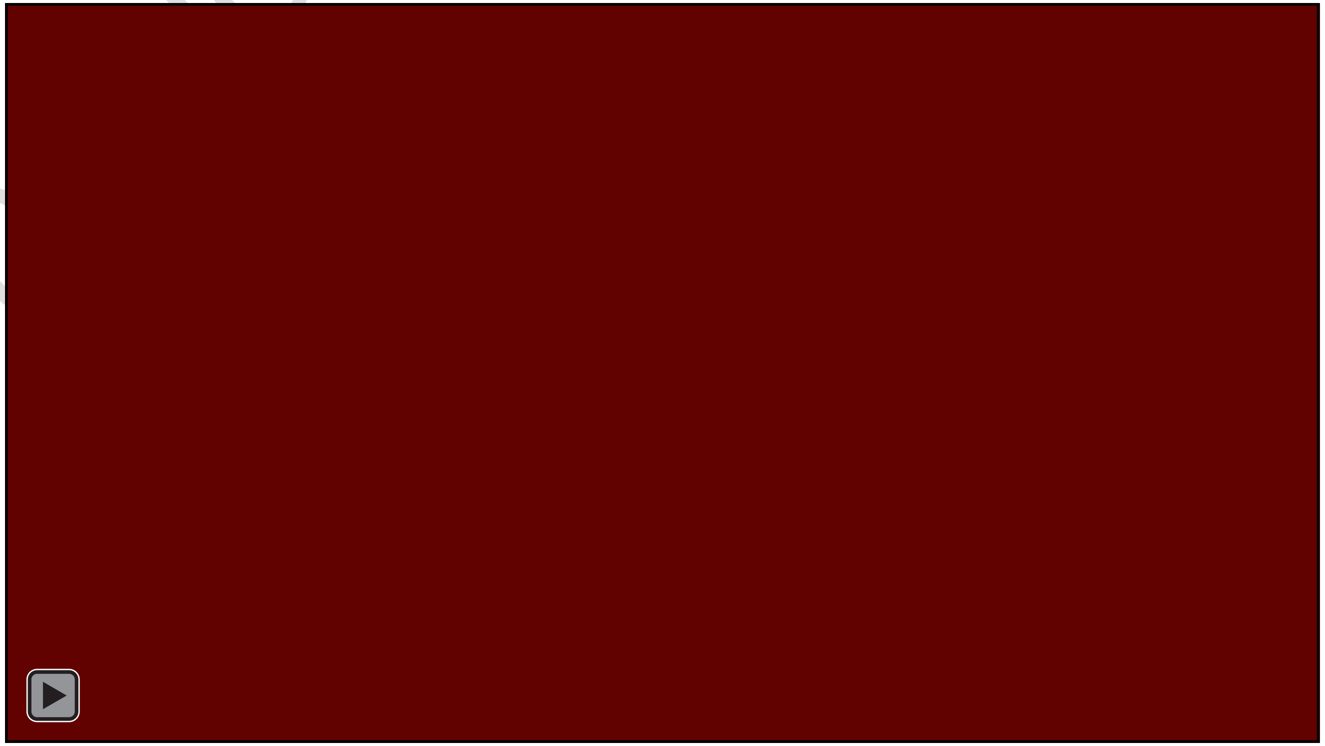




Robot-guided TMS

- Target different network nodes in specific order and timing
- Adaptive close loop system

Axilum Robotics



FDA Cleared Devices for

Medication-Resistant Depression
Adolescent depression
Migraine
OCD
Substance Abuse D/O
Anxiety D/O

Growing list of off-label applications

PTSD
Bipolar disorder
Autism
Pain
Parkinson's Disease
Focal Epilepsy
Impulse control D/O
Agitation
MCI & Dementia

NEURONETICS

magstim

eNeura

Brainsway

MagVenture

Nexstim

Real Clinical Impact !

TMS in Medication-Resistant Depression

- >600 systems in clinical use in the US
- 250 days/year & 5 patients/day

= *750,000 treatments per year*

- approx. 25 sessions/Rx/patient

= *30,000 patients/year*

- 30% remission

= *9,000 patients in remission/year*

➢ ***25 patients in remission/day***

Covered by Medicare
& most health insurance plans in the US

Covered by health insurance in
- Canada
- Australia
- New Zealand
- Japan
- UK

Real Clinical Impact !

TMS in Medication-Resistant Depression

- After a treatment course (of up to 6 weeks) benefit lasts on average 5 months
- In case of relapse, response to new treatment course is at least as good as initial response in >90% of cases [Kelly et al. J Neuropsych Clin Neurosci 2017]
- Maintenance is possible

Helping Patients
However……only the beginning

Realize the Promise of Neuromodulation

Noninvasive Neuromodulation does not represent a treatment for an illness, but offers **tool** that allows modulation of the neural substrate of **symptoms and disabilities** caused by brain illnesses or dysfunctions

Helping Patients
However……only the beginning

Realize the Promise of Neuromodulation

PRECISION
- Competencies & Training
- Safety
- Spatio-temporal signatures of brain-related disability
- Target specific symptoms/disabilities
- Leverage individual differences

IMPORTANCE OF MODELLING • NEW TECHNOLOGIES • SCALABILITY
- Home
- New Technologies
- Targeting specific symptoms/disabilities

Clinical Neurophysiology 120 (2009) 2008–2039

Contents lists available at ScienceDirect

Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

Guidelines

Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research ☆

Simone Rossi [a,*], Mark Hallett [b], Paolo M. Rossini [c,d], Alvaro Pascual-Leone [e] and The Safety of TMS Consensus Group [1]

Clinical Neurophysiology 132 (2021) 269–306

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Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

Review

Safety and recommendations for TMS use in healthy subjects and patient populations, with updates on training, ethical and regulatory issues: Expert Guidelines

Simone Rossi [a,*], Andrea Antal [b,c], Sven Bestmann [d], Marom Bikson [e], Carmen Brewer [f], Jürgen Brockmöller [g], Linda L. Carpenter [h], Massimo Cincotta [i], Robert Chen [j], Jeff D. Daskalakis [k], Vincenzo Di Lazzaro [l], Michael D. Fox [m,n,o], Mark S. George [p], Donald Gilbert [q], Vasilios K. Kimiskidis [r], Giacomo Koch [s], Risto J. Ilmoniemi [t], Jean Pascal Lefaucheur [u,v], Letizia Leocani [w], Sarah H. Lisanby [x,y,2], Carlo Miniussi [z], Frank Padberg [aa], Alvaro Pascual-Leone [ab,ac,ad], Walter Paulus [b], Angel V. Peterchev [ae], Angelo Quartarone [af], Alexander Rotenberg [ag], John Rothwell [d], Paolo M. Rossini [ah], Emiliano Santarnecchi [m], Mouhsin M. Shafi [m], Hartwig R. Siebner [ai,aj,ak], Yoshikatzu Ugawa [al], Eric M. Wassermann [am,2], Abraham Zangen [an], Ulf Ziemann [ao], Mark Hallett [ap,2,*]

The basis of this article began with a Consensus Statement from the IFCN Workshop on "Present, Future of TMS: Safety, Ethical Guidelines", Siena, October 17-20, 2018, updating through April 2020 [1]

Clinical Neurophysiology 132 (2021) 819–837

Contents lists available at ScienceDirect

Clinical Neurophysiology

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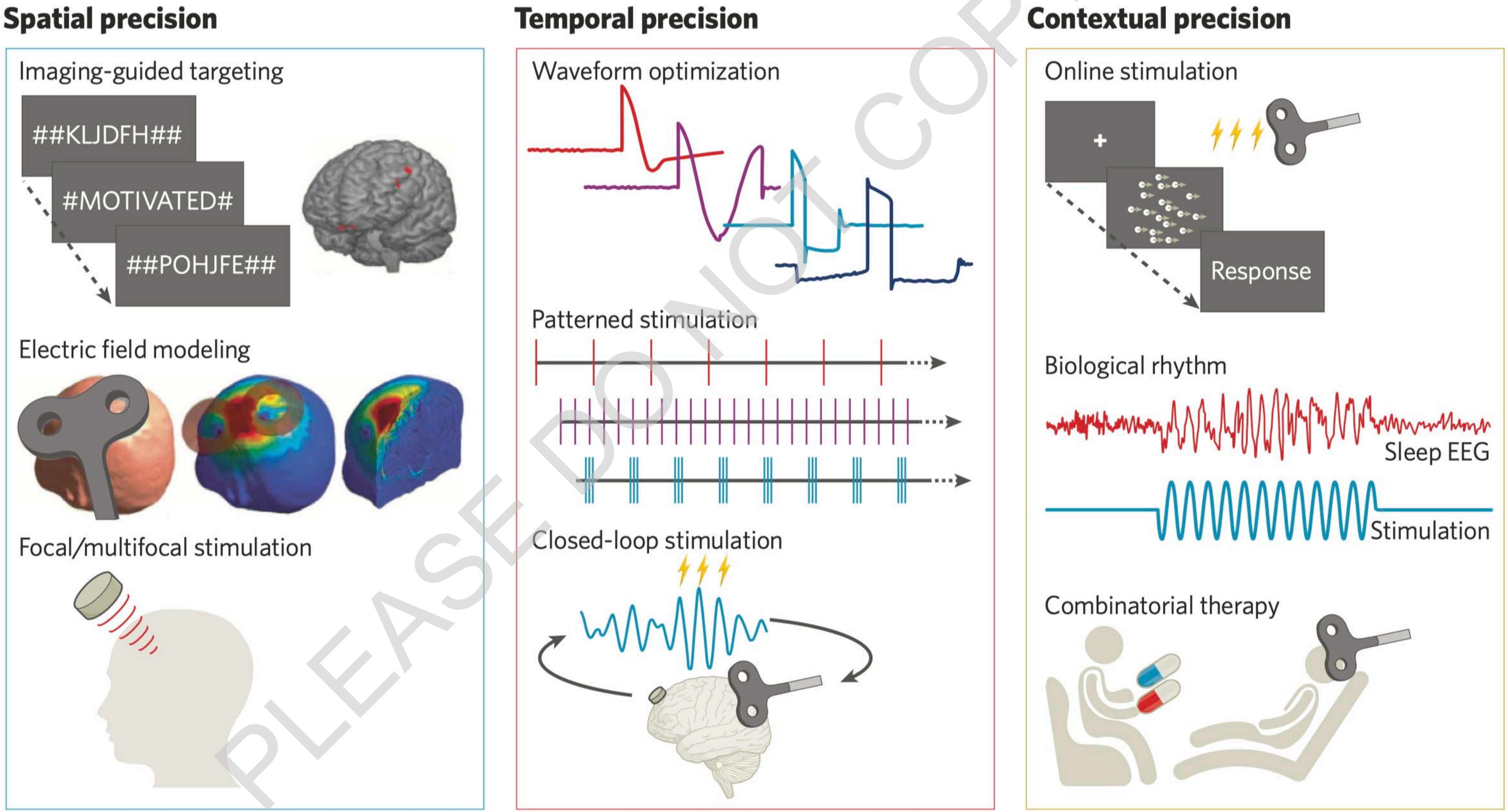
Review

Training in the practice of noninvasive brain stimulation: Recommendations from an IFCN committee

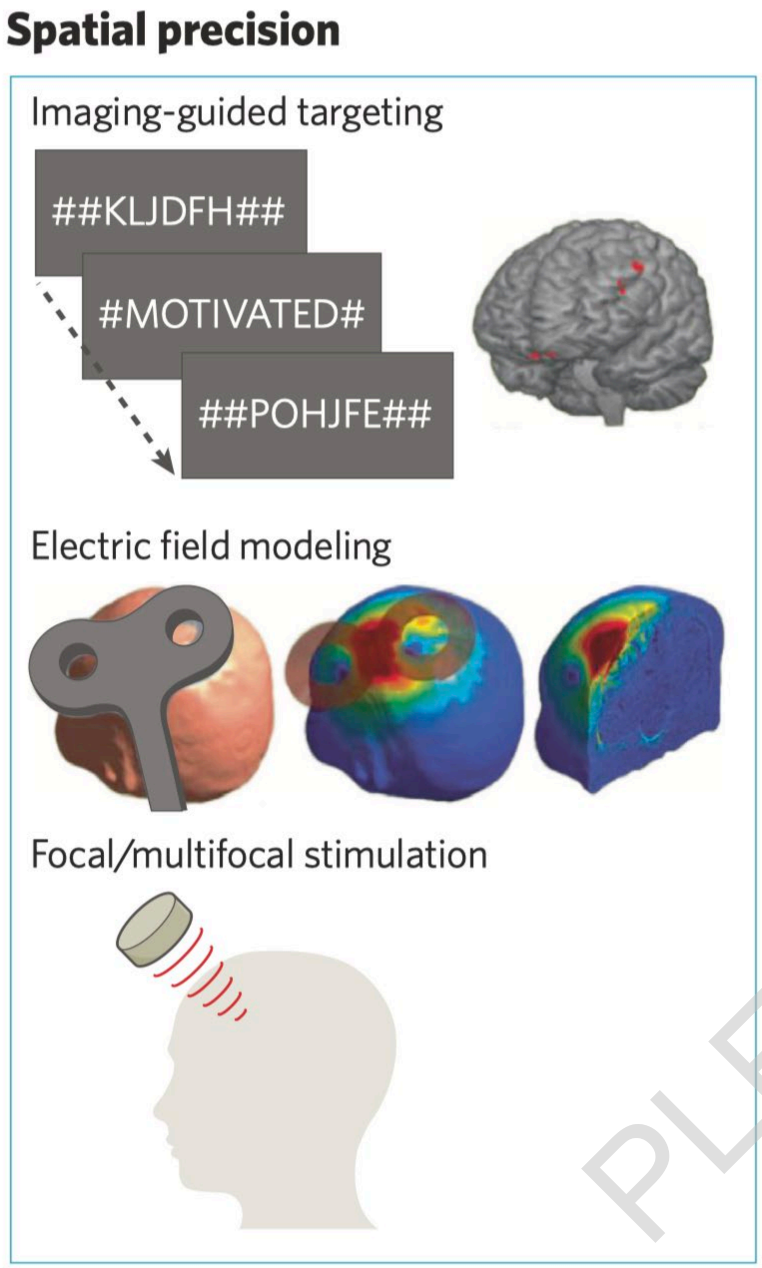
Peter J. Fried [a,1], Emiliano Santarnecchi [a,1], Andrea Antal [b], David Bartres-Faz [c], Sven Bestmann [d], Linda L. Carpenter [e], Pablo Celnik [f], Dylan Edwards [g,h], Faranak Farzan [i], Shirley Fecteau [j], Mark S. George [k,l], Bin He [m], Yun-Hee Kim [n], Letizia Leocani [o], Sarah H. Lisanby [p], Colleen Loo [q], Bruce Luber [r], Michael A. Nitsche [s], Walter Paulus [b], Simone Rossi [t], Paolo M. Rossini [u], John Rothwell [v], Alexander T. Sack [w], Gregor Thut [x], Yoshikazu Ugawa [y], Ulf Ziemann [z], Mark Hallett [aa], Alvaro Pascual-Leone [ab,ac,*]

Realize the Promise of Neuromodulation

PRECISION



Jannati et al. Neuropsychopharmacology 2023

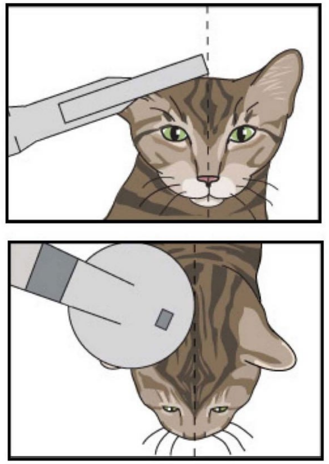


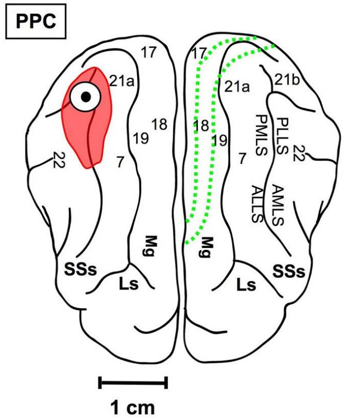
1. Know where to target
   - MRI-guided TMS

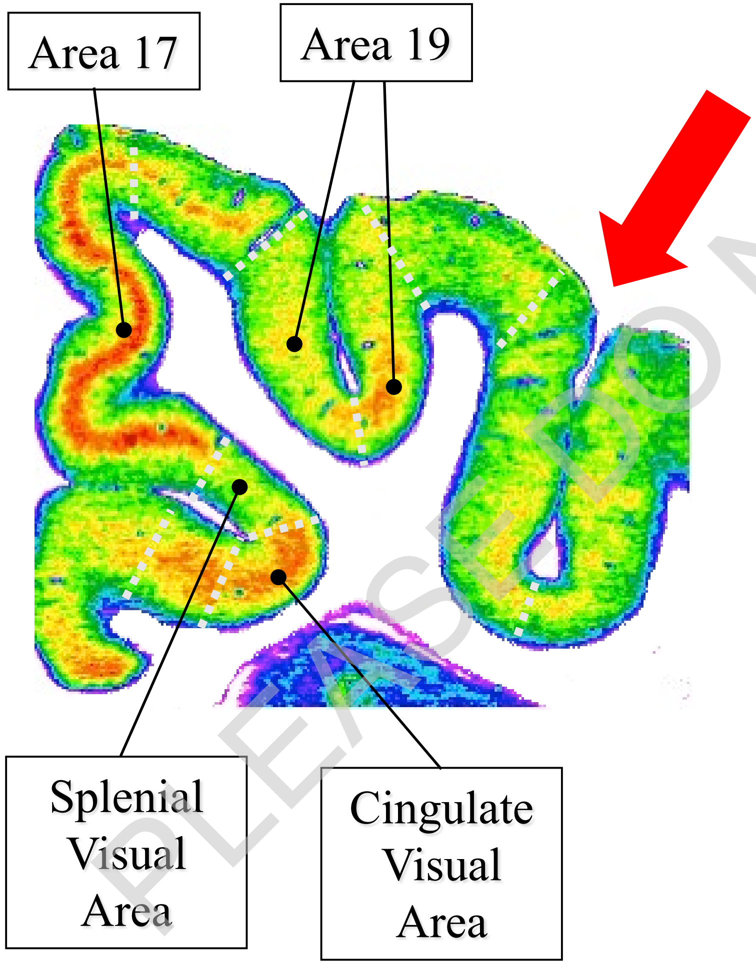
2. Keep target consistent
   - Robot-assisted TMS

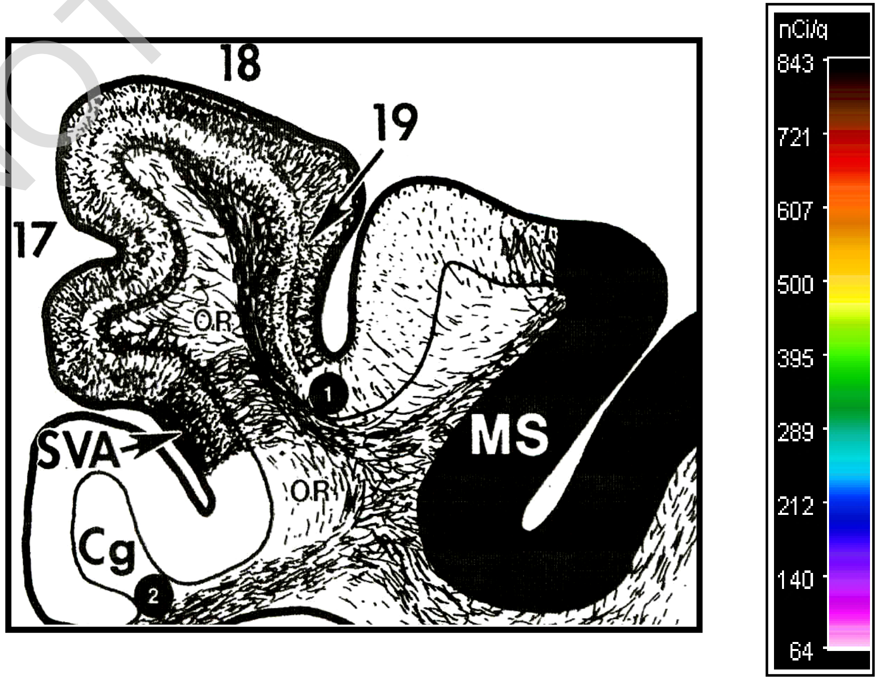
3. Make target smaller
   - Micro TMS

NiBS modulates activity in brain networks & the effects depend on connectivity



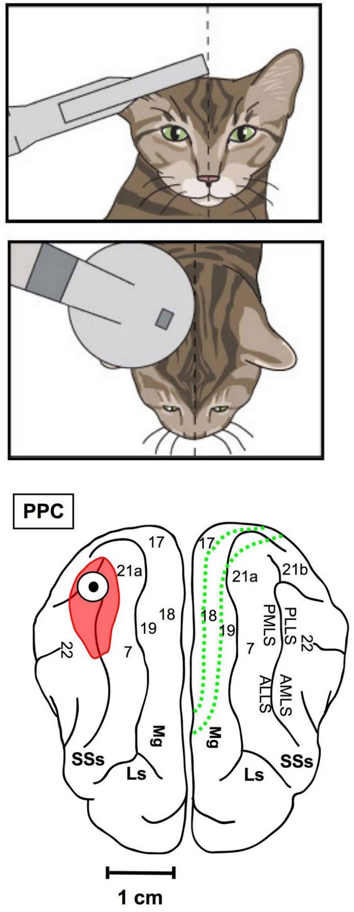


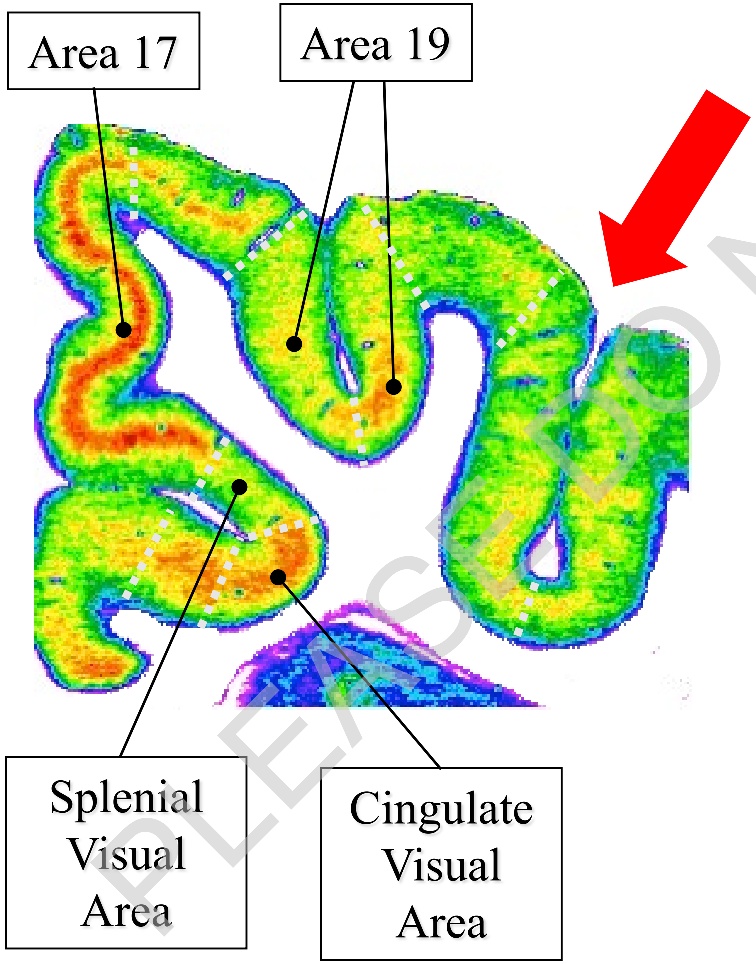


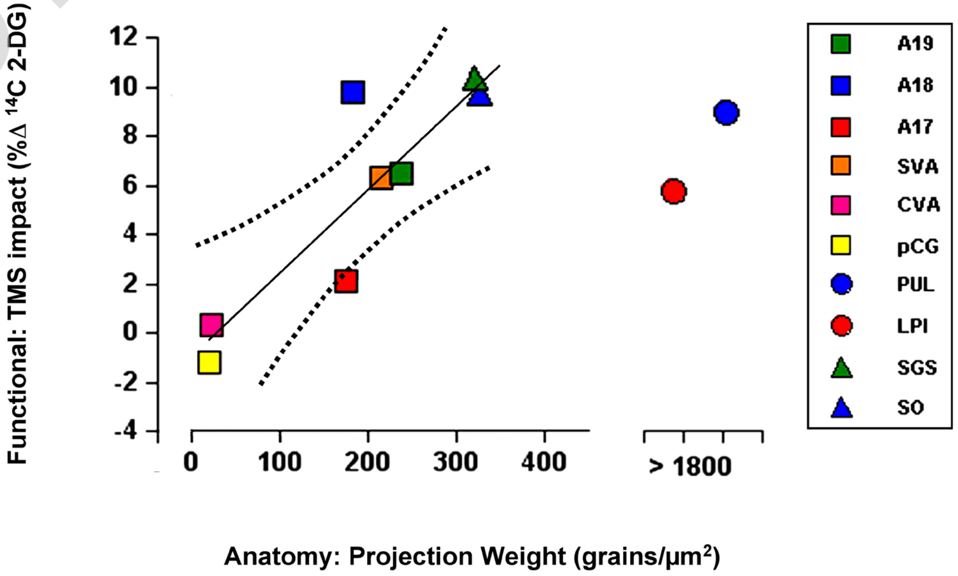


Valero-Cabre et al *Exp Brain Res 2005, 2006*

NiBS modulates activity in brain networks & the effects depend on connectivity





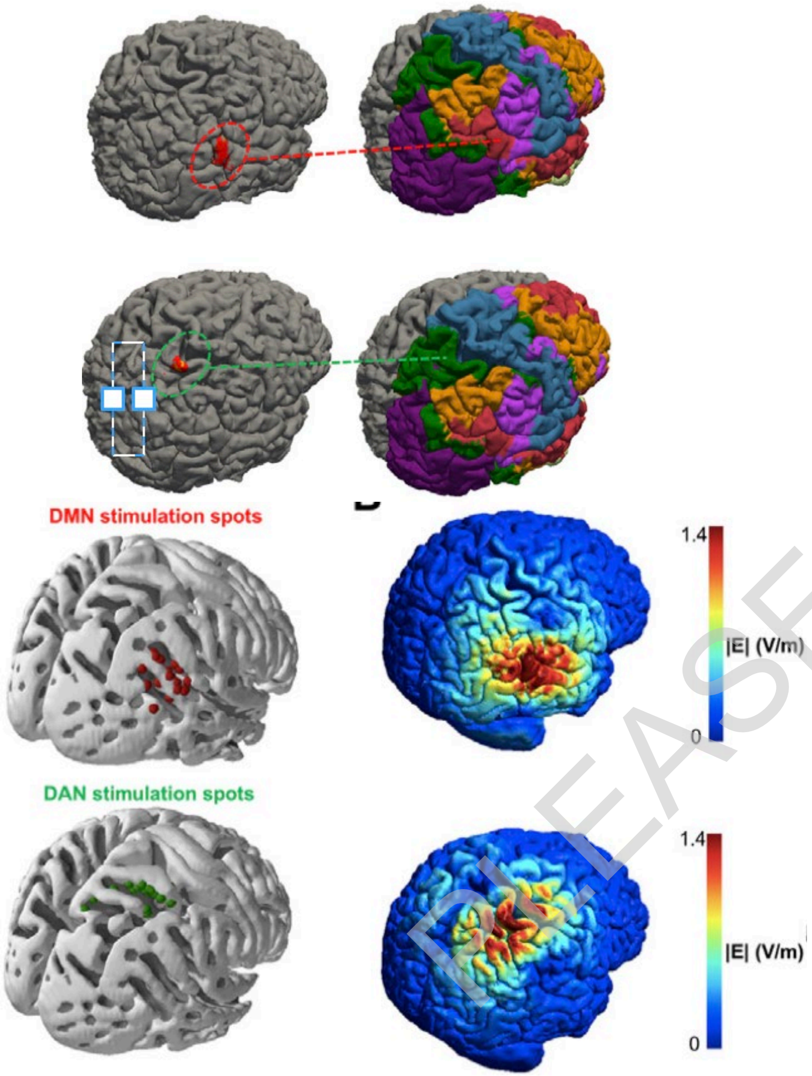


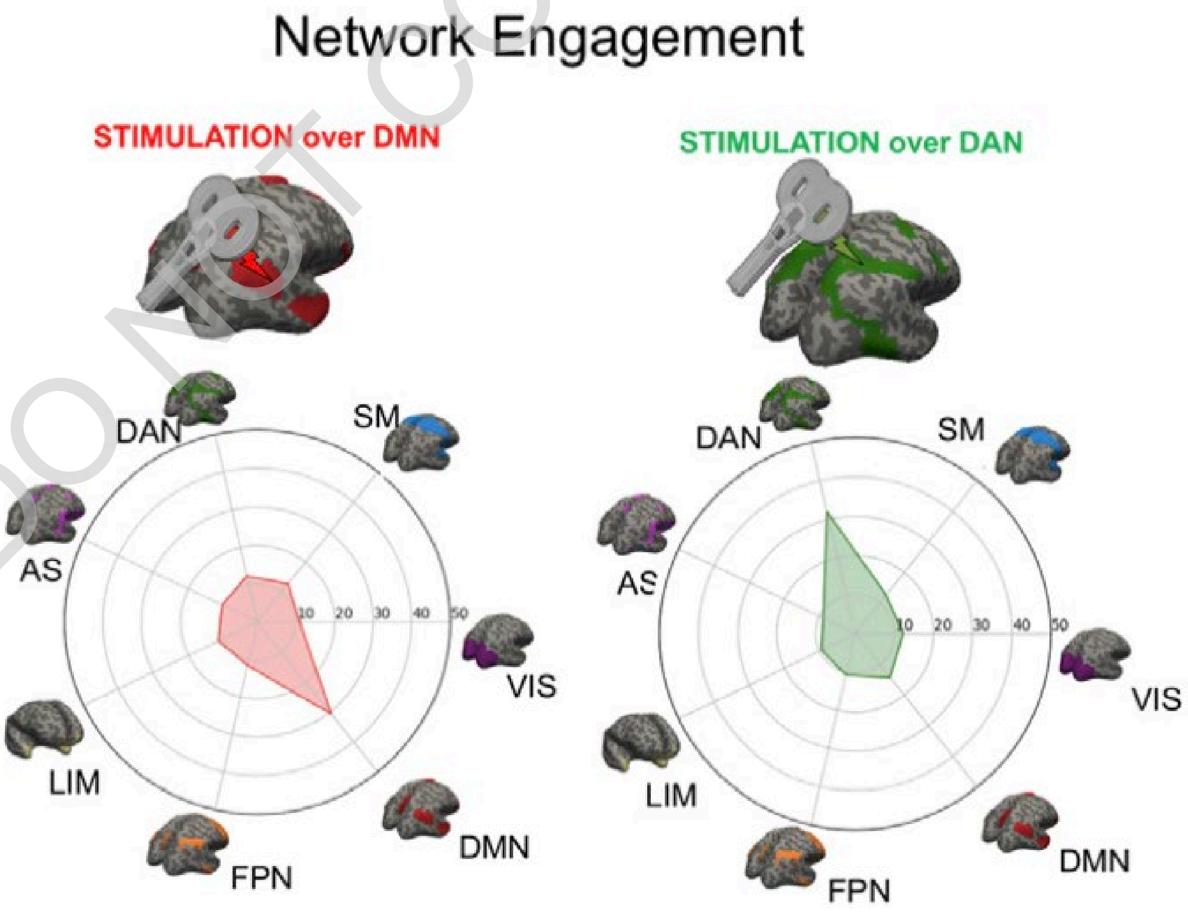
Valero-Cabre et al *Exp Brain Res 2005, 2006*

Momi et al. Neuroimage 2021

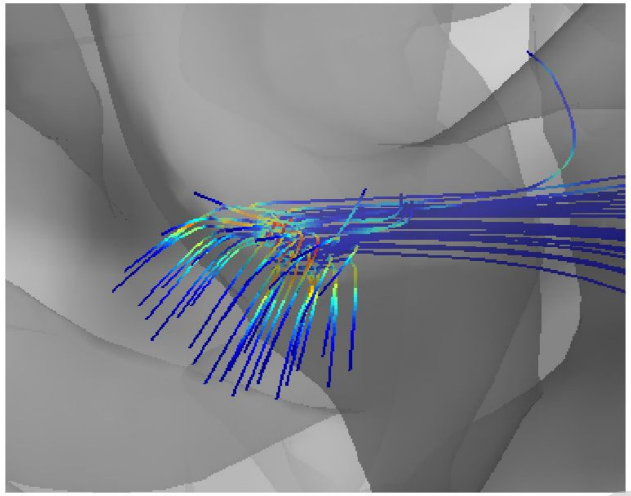
Impact on specific brain networks

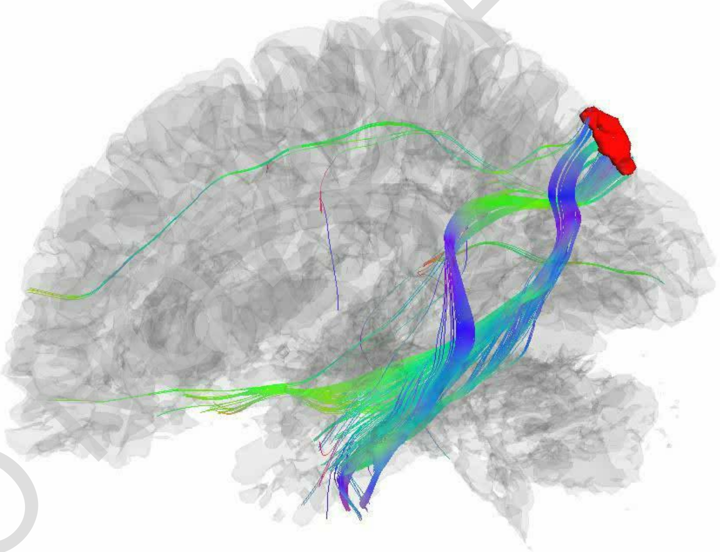
Davide
Momi

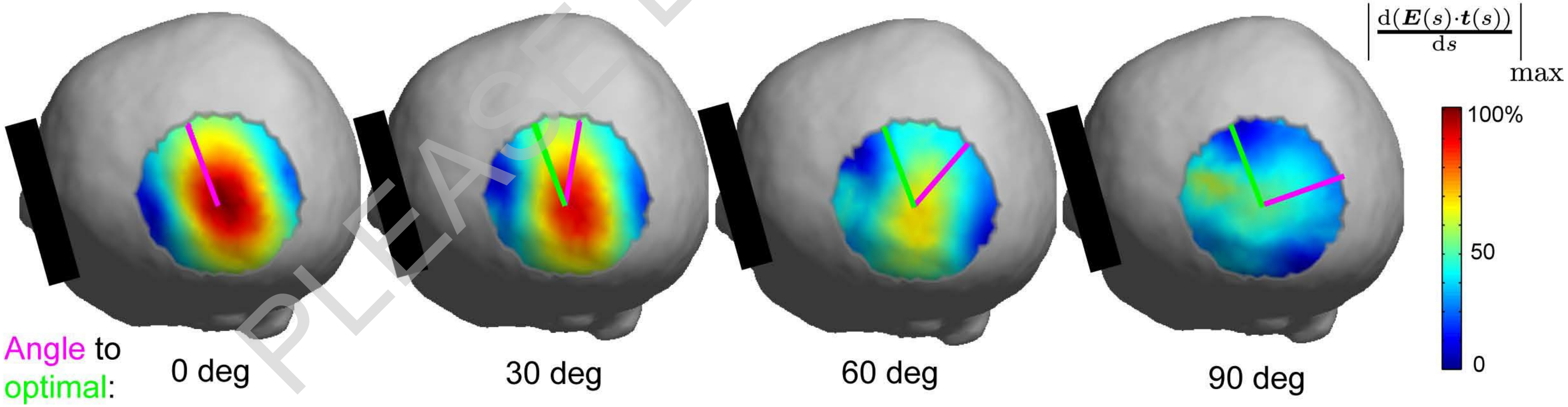




The effect of coil orientation





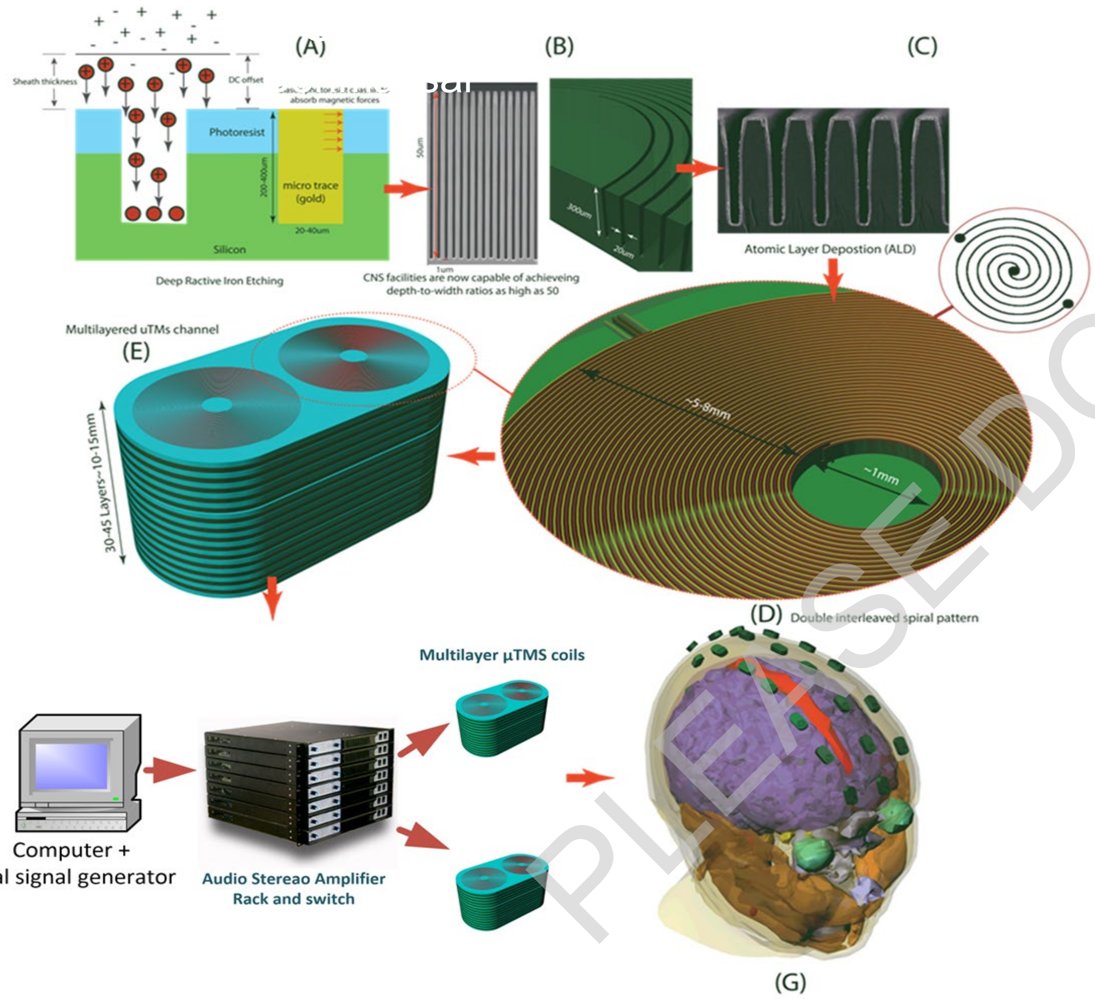


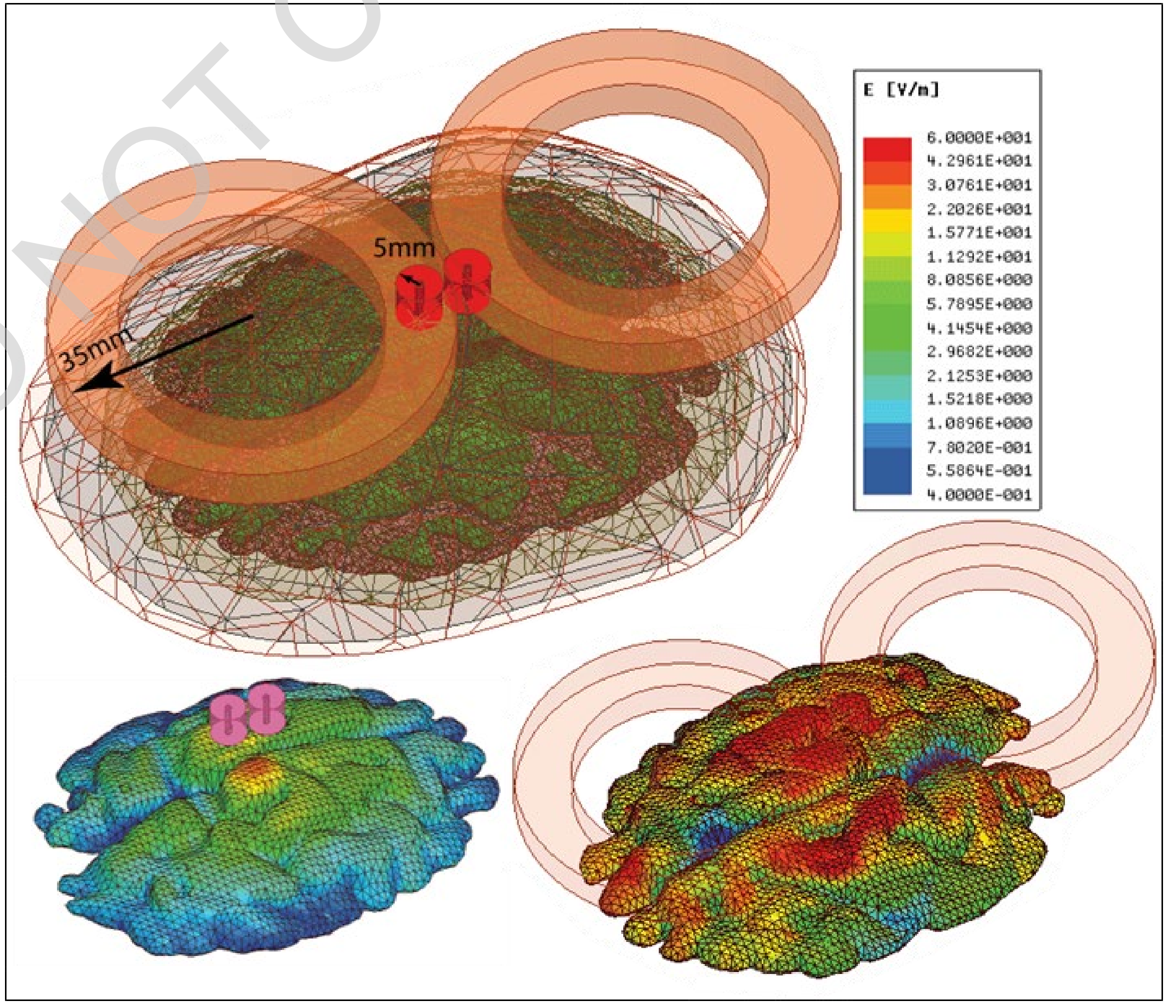
Nummenmaa et al *Neuroimage* 2013

µTMS

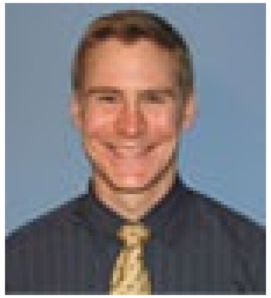
Annu Int Conf IEEE Eng Med Biol Soc. 20

Giorgio Bonmassar

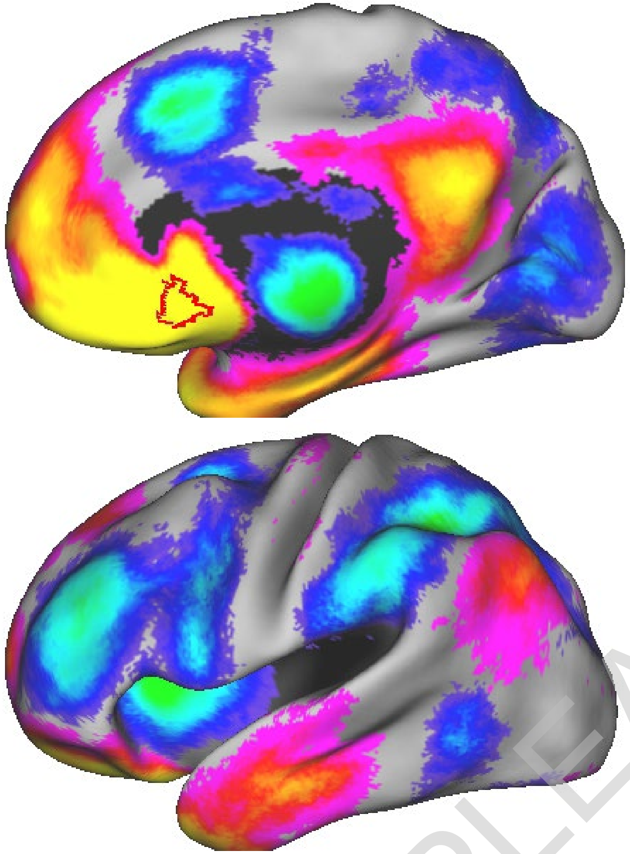




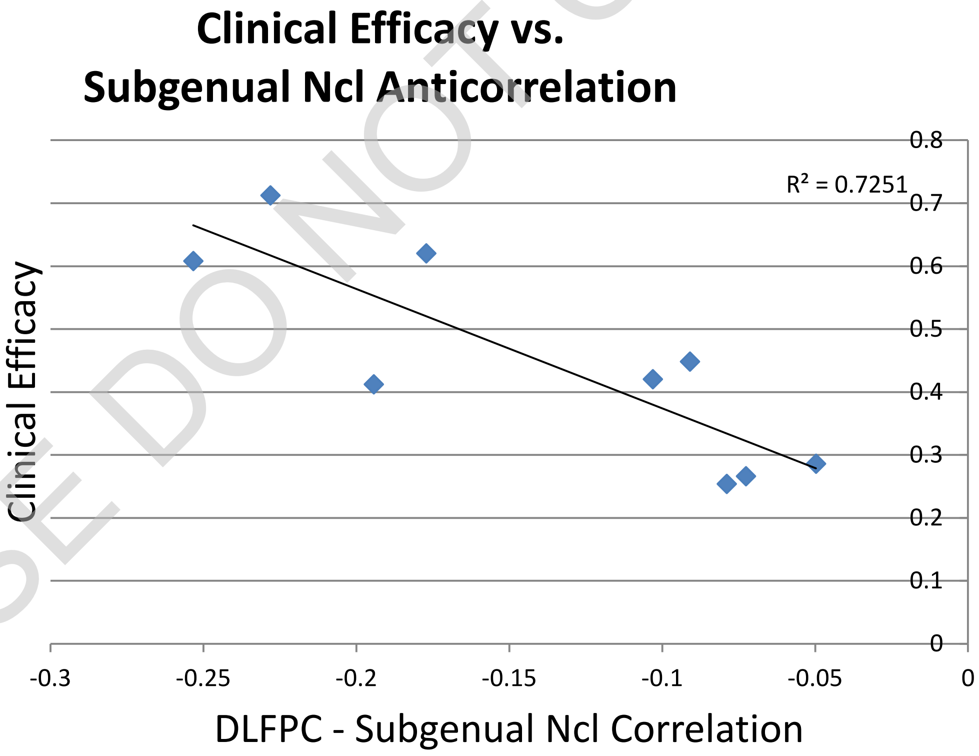
Brain Target and Need to Individualize

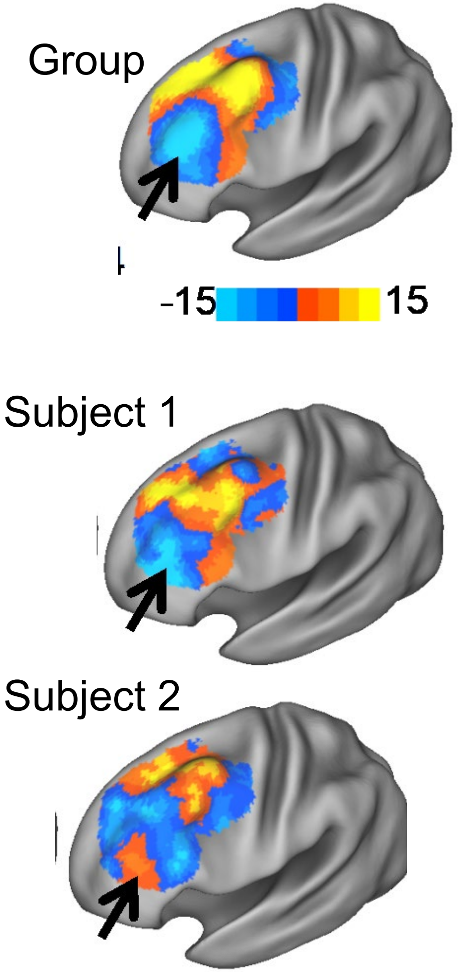


Mike Fox

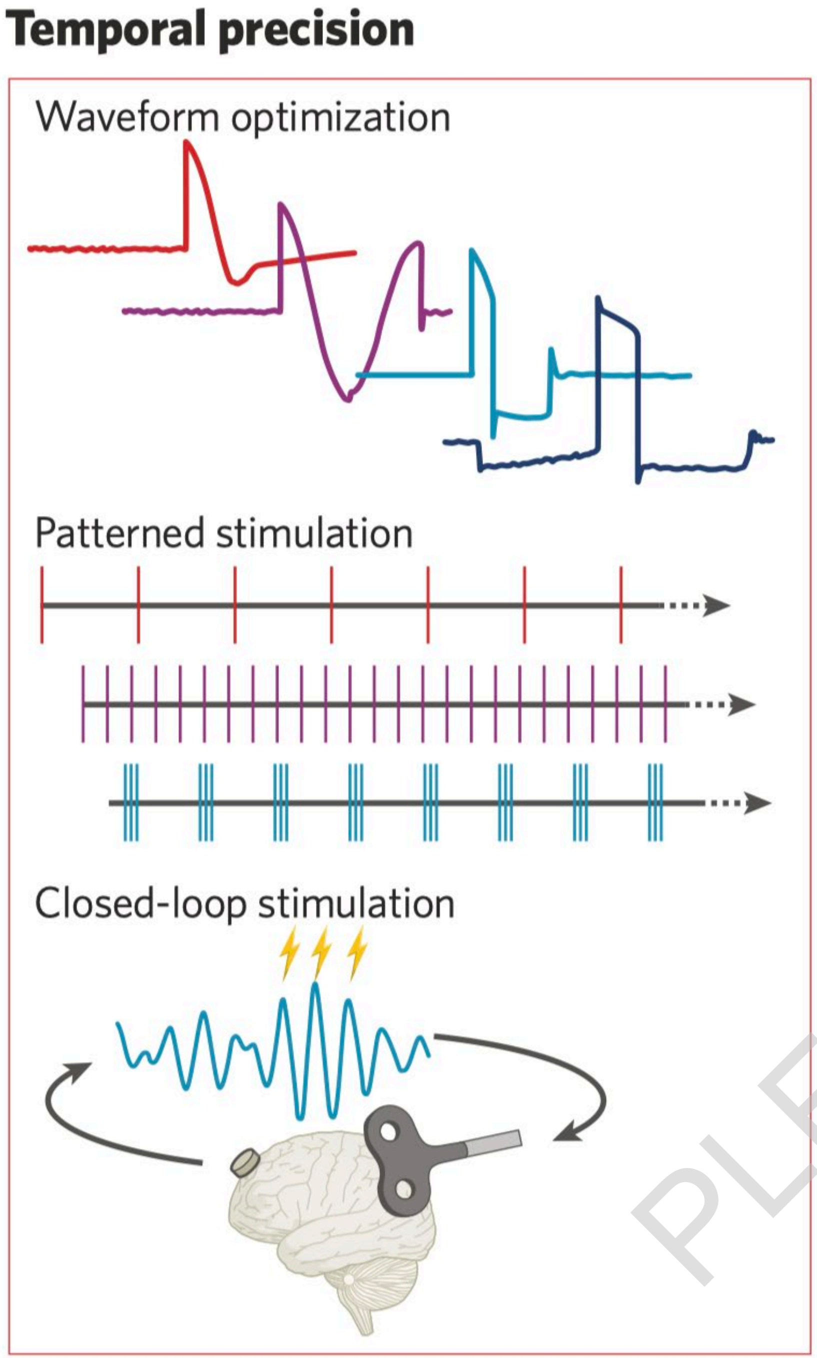


rs-fcMRI connectivity





Fox et al *Biological Psych* 2012; *Neuroimage* 2013
Weigand et al. *Biological Psych* 2018



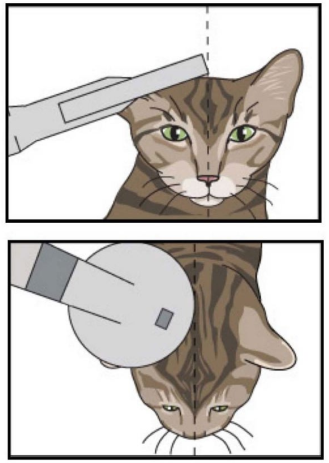
1. Individualize stimulation parameters
    - Measure neurophysiologic effect

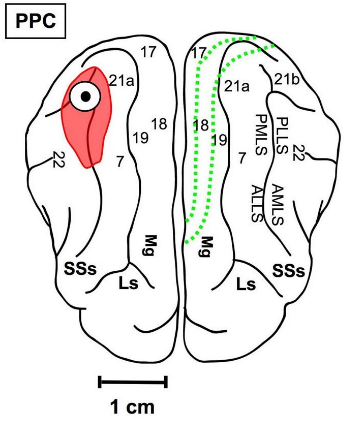
2. Design improved stimulators

3. Stimulate at right time
    - Closed loop stimulation

rTMS modulates activity in targeted brain beyond the duration of the stimulation & depending on stimulation frequency

Antoni Valero-Cabré

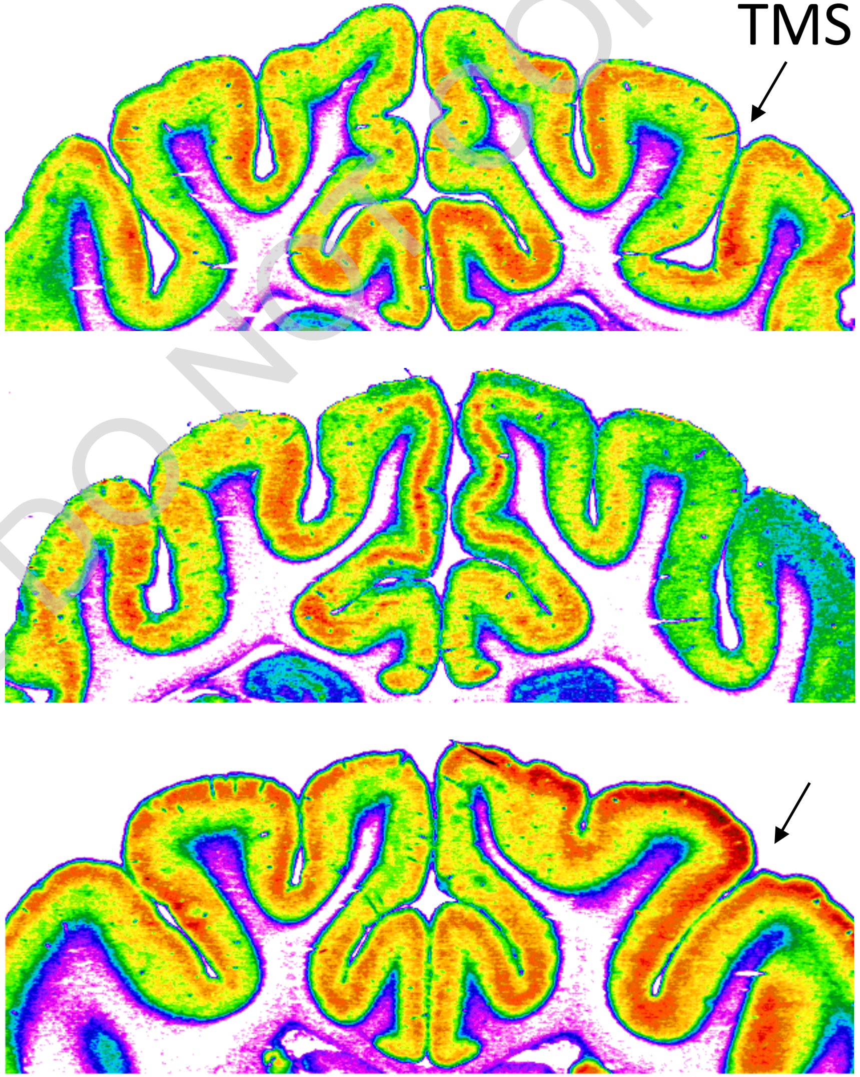


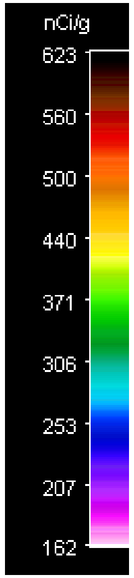


Sham TMS

1 Hz TMS

20 Hz TMS

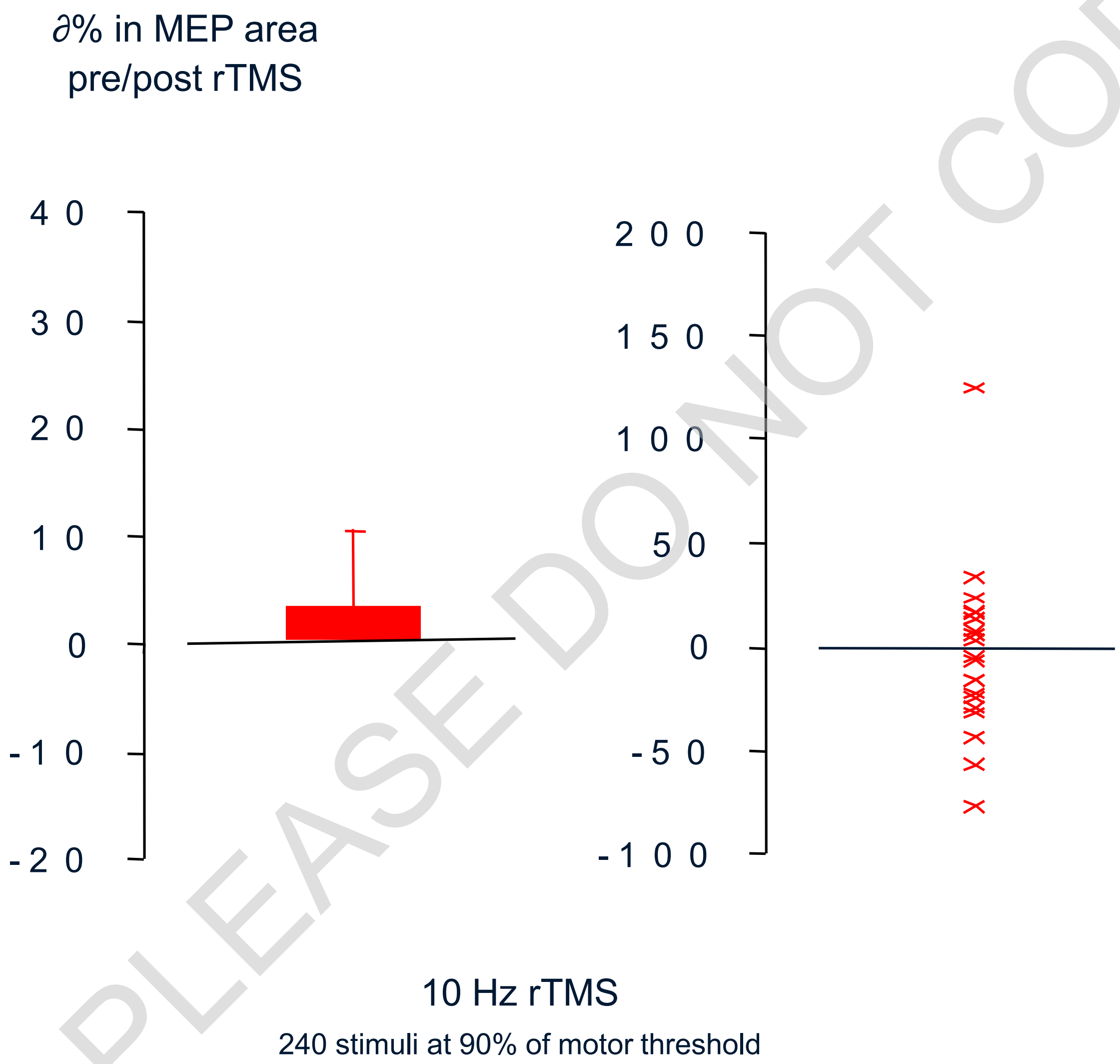




Valero-Cabre et al *Exp Brain Res 2005, 2006*

Variability of Physiologic Effects

Fumiko
(Maeda) Hoeft

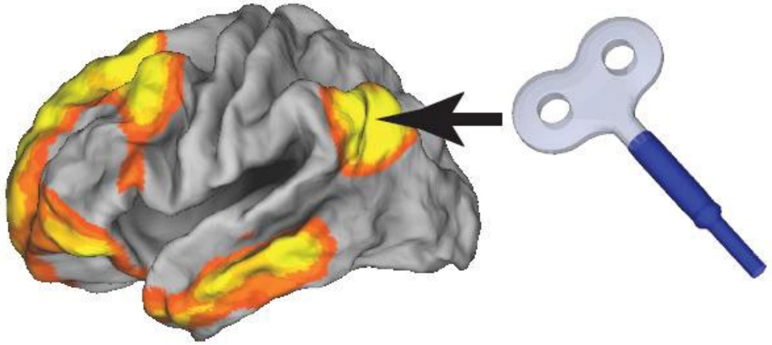


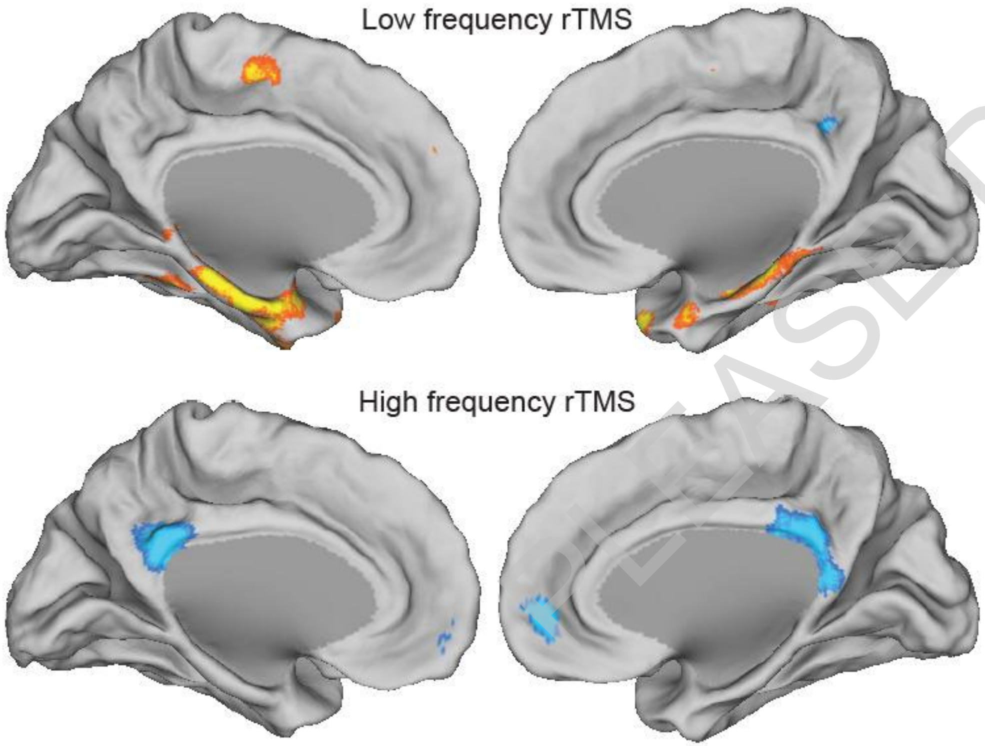
There is no 'inhibitory' or 'excitatory' rTMS

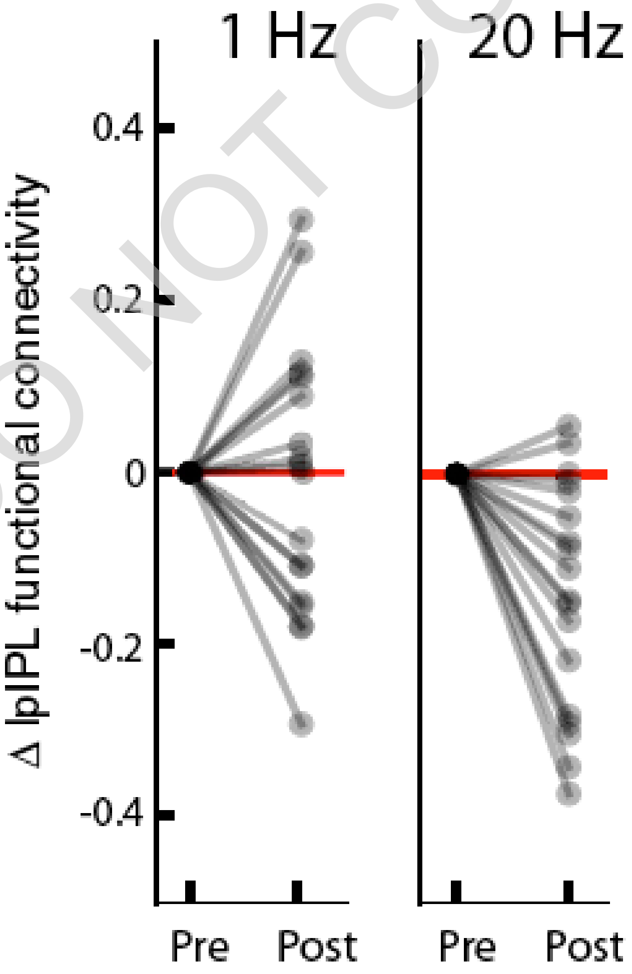
Maeda et al, 2000

Variability of Physiologic Effects

Mark Eldaief







Need to Measure!

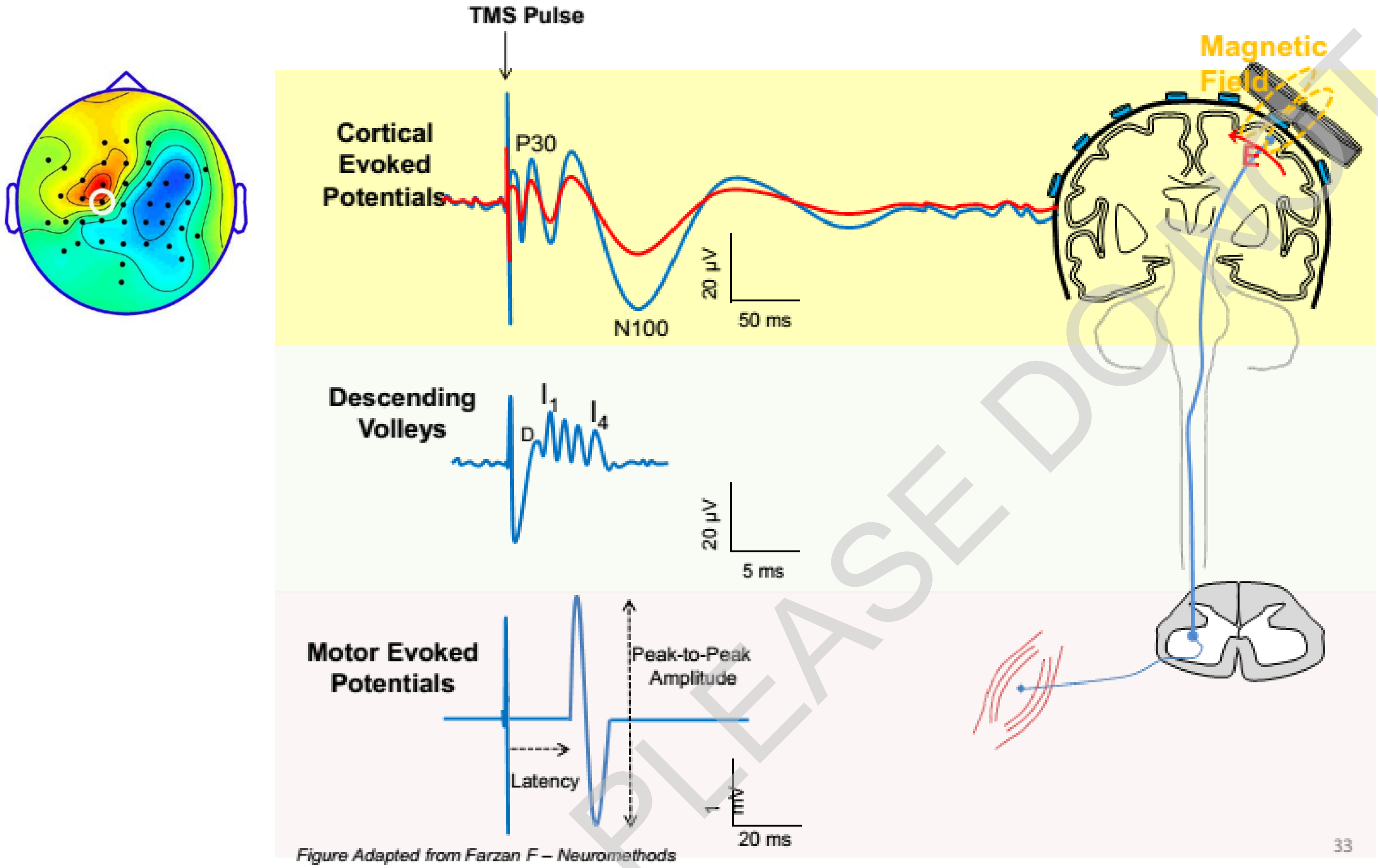
Neurophysiologic monitoring:
fMRI – EEG – etc

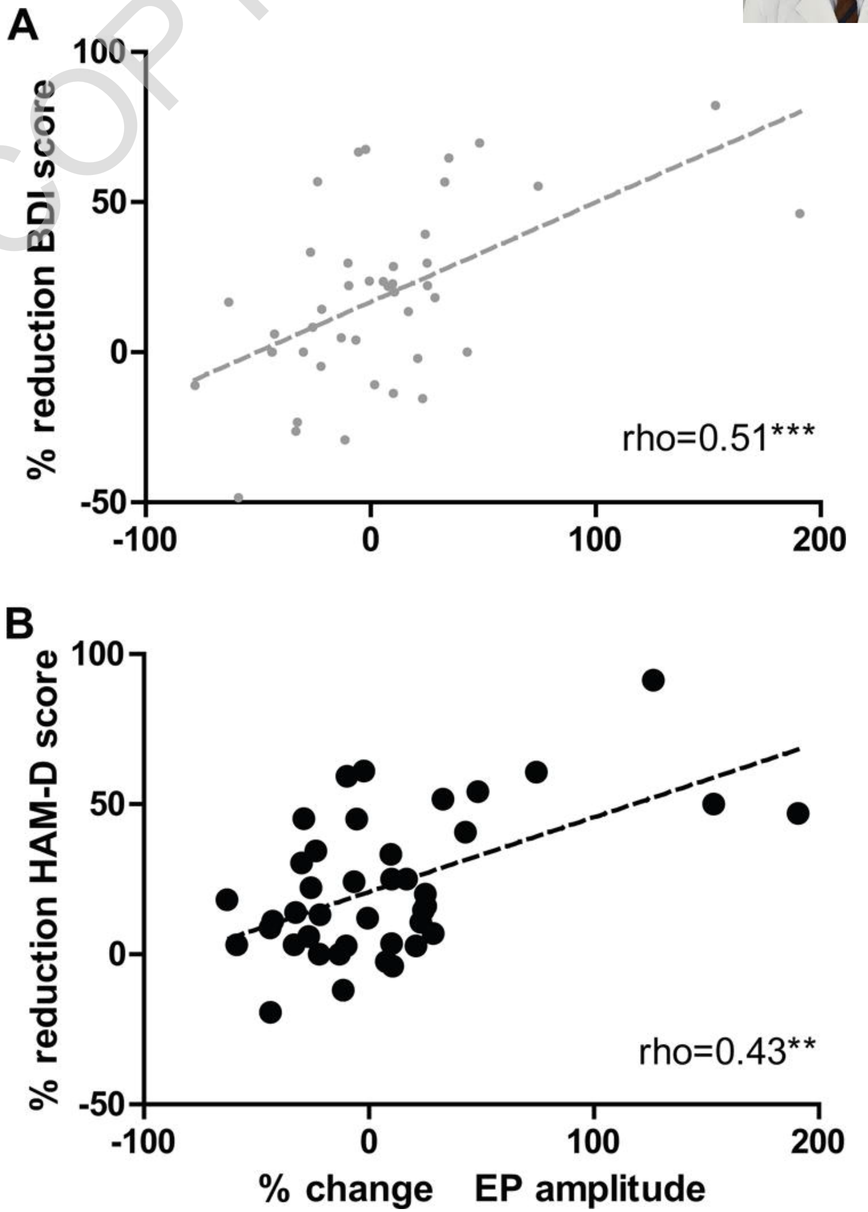
Define dose
Enable close-loop

Eldaief et al *PNAS*, 2011

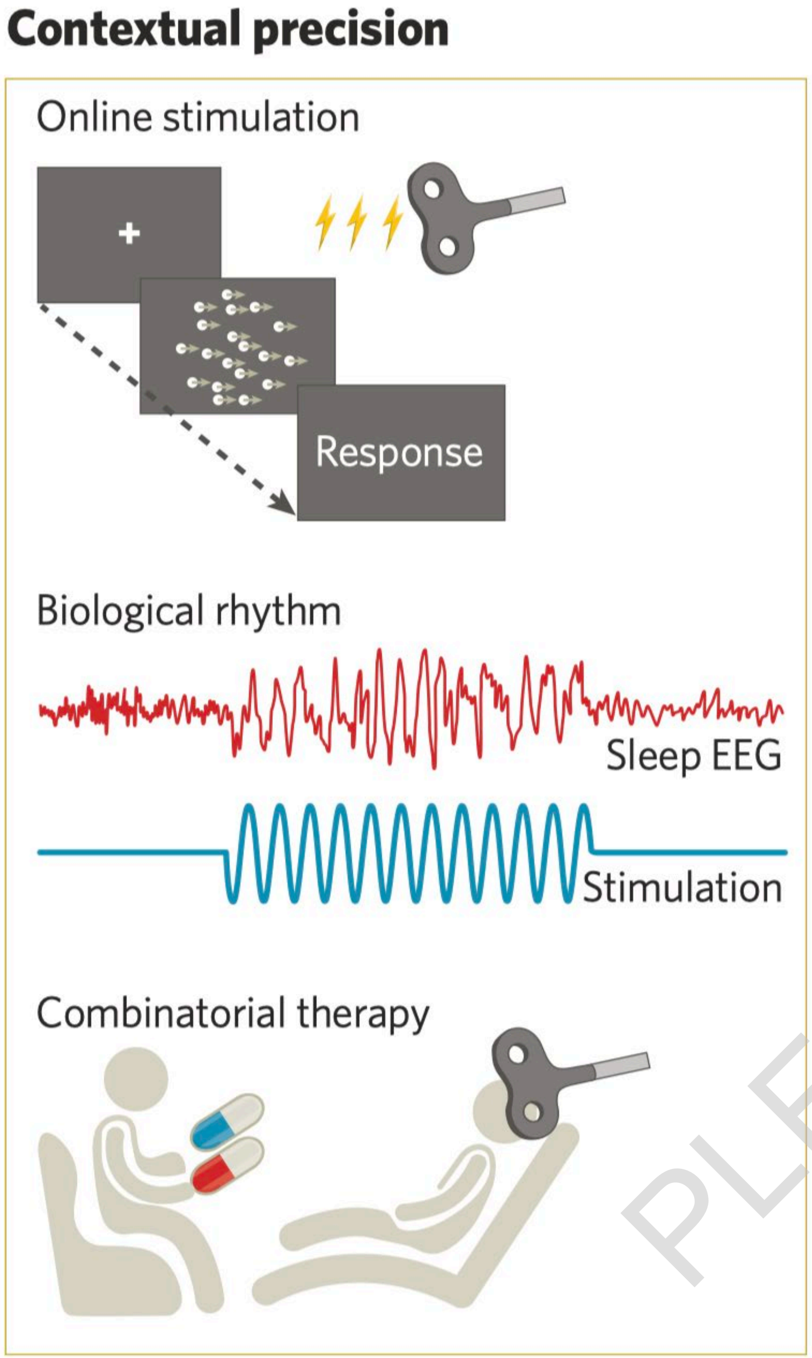
Albino
Oliveira-Maia

Neurophysiologic Biomarkers Predict Clinical Response





Oliveira-Maia et al *Brain Stimulation*, 2017



1. Stimulate at right time
   - Closed loop stimulation

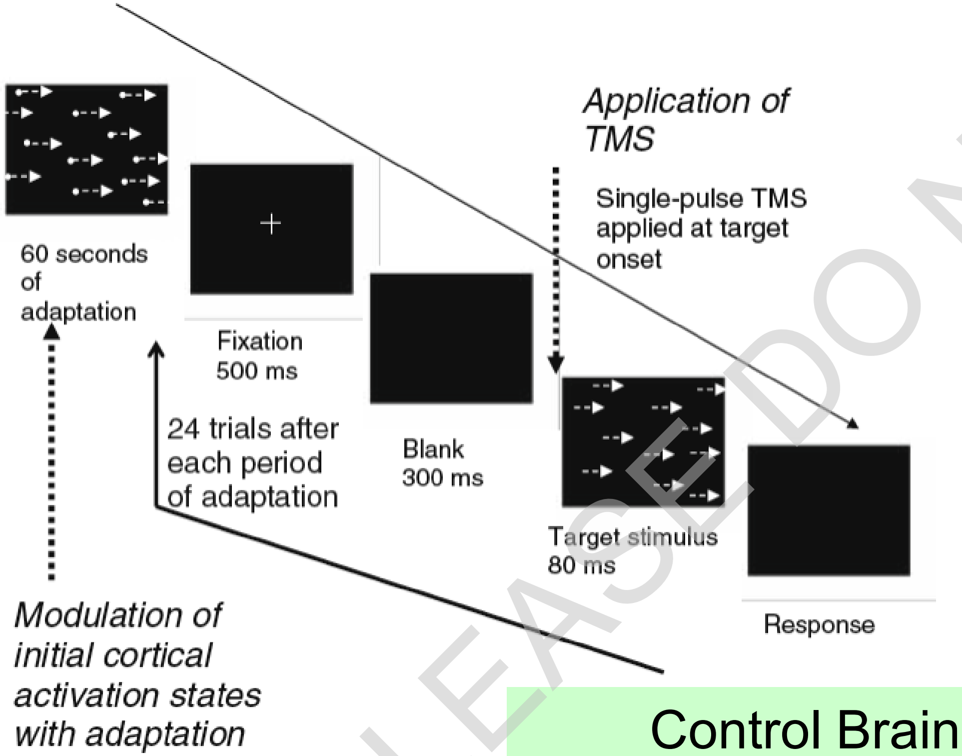
2. Leverage State-dependency effects

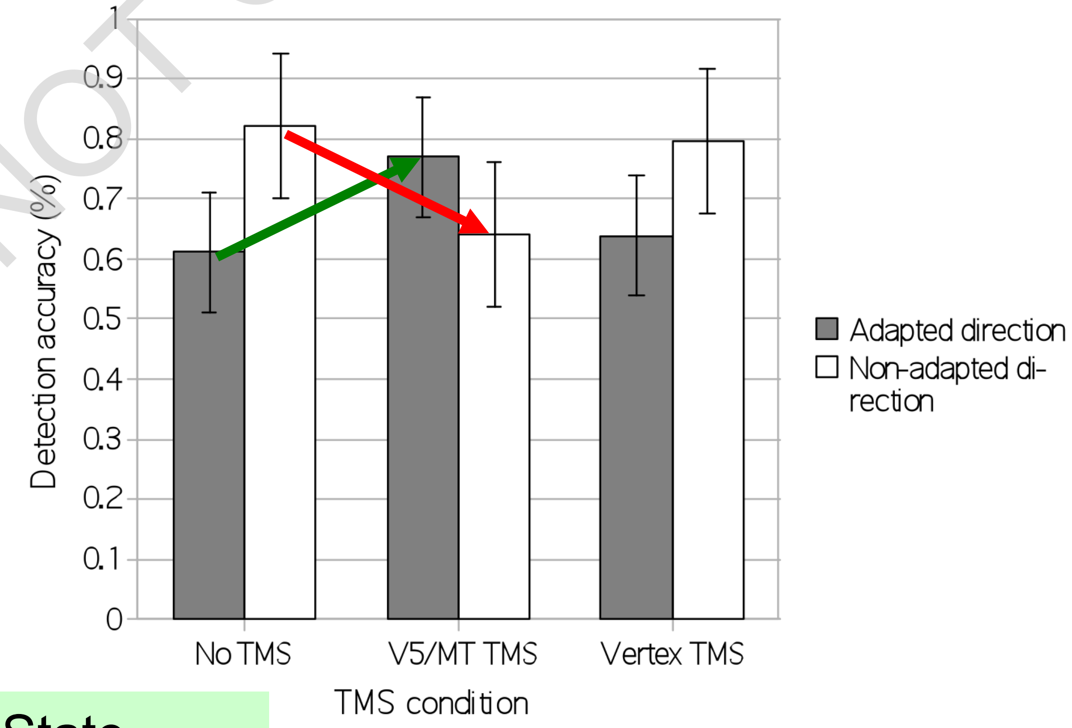
Zaira Cattaneo

Juha Silvanto

State Dependency For Specific Neural Populations

TMS-adaptation paradigm and motion direction discrimination in visual area V5/MT





Control Brain State

Consistency and Greater Specificity of Effect

TMS disrupts non-adapted but improves adapted direction discrimination

Cattaneo & Silvanto *Neurosci Lett* 08

Brain Topogr (2008) 21:1–10
DOI 10.1007/s10548-008-0067-0

REVIEW ARTICLE

State-Dependency of Transcranial Magnetic Stimulation

Juha Silvanto · Alvaro Pascual-Leone

Concurrent TMS stimulation with
Cognitive Training in Dementia

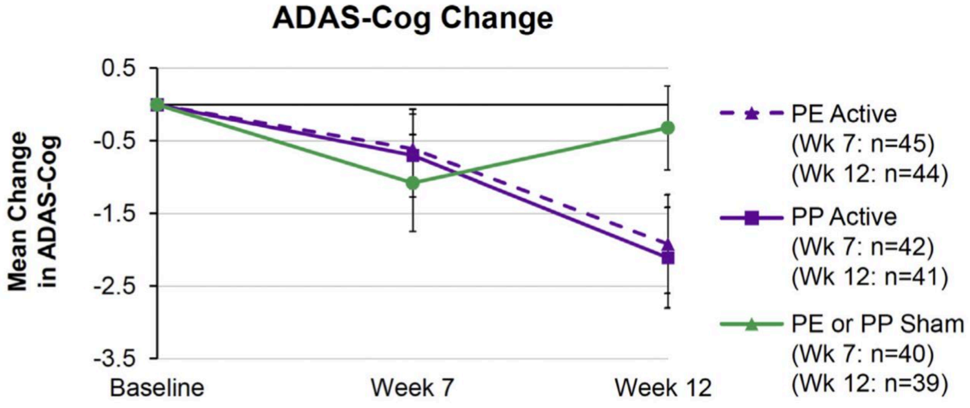
Sabbagh et al *Alzheimer's & Dementia* 2019

NEURONIX
INTEGRATING NEUROLOGICAL SOLUTIONS

FDA-Approval for OCD
Provocation task + TMS

Brainsway

- How create an 'optimal' state ?
- When to couple brain stimulation with state modification ?



Factors Contributing to Individual Variability

- Genetics
  - BDNF met/val
- Age
  - Age-related GABA effect
- Head shape
  - Asian vs Caucasian
- IQ, Cognitive Capacity
- Brain structure
  - Atrophy
  - Connectivity

Leverage Individual Differences instead of trying to Control them?

- Circadian rhythms
  - Time of day
- Hormonal state
  - Menstrual cycle
- Metabolic state
  - Low K+ (diarrhea)
- Nutrition considerations
  - Coffee
- Medications
  - Valproate
- State / Mindset

TMS Basics

- Misnomer
- Stimulation to brain interaction
  - Brain structure
  - Brain state
- Pulse shape
- Single pulse
- Pairs of pulses
- Trains of repetitive pulses
- Variability

- Electrodeless Electric Stimulation via Electromagnetic Induction
- There is no FOCAL TMS – CIRCUIT THERAPEUTICS
  - Not a treatment for a disease – but for symptoms/disabilities
  - Cortical target as 'window' – leverage brain network knowledge
- There is no INHIBITORY or EXCITATORY TMS
  - There are huge interindividual differences
  - Need to measure – relate behavioral to physiologic effects
- Effects depend on brain state – STATE DEPENDENCY is critical
  - Use state dependency for greater effect specificity

REMEMBER:

- Details matter (coil size and shape, pulse shape, current direction, etc.)
  - More is not necessarily better – NEUROPHYSIOLOGIC PRECISION
- Test-rest reliability is poor and should be assessed
- Sham stimulation is tricky – ACTIVE controls